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Scholarly Review

Sex Differences in Depression as a Risk Factor for Alzheimer's Disease: A Systematic Review

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Abstract

Background and Objectives: Depression is an important risk factor for Alzheimer's disease (AD) but little is known about the mechanisms of this association. Given sex differences in both AD and depression, we sought to conduct a systematic review and meta-analysis to examine whether there are sex differences in their association, as this may improve understanding of underlying mechanisms.

Research Design and Methods: MEDLINE, PsycINFO, and Cochrane Reviews were searched for observational studies including both sexes and examining the association between history of depression and AD.

Results: Forty studies, including 62,729 women and 47,342 men, were identified. Meta-analysis was not possible because only 3 studies provided sufficient data. Seven studies provided information about the influence of sex for a qualitative synthesis. Two found an association in men only, 2 in women only, and 3 reported no sex differences. The 2 studies finding an association in women only were unique in that they had the shortest follow-up periods, and were the only clinic-based studies.

Discussion and Implications: The findings of our systematic review show that there are important methodological differences among the few studies providing data on the influence of sex on depression as a risk factor for AD. Had all 40 studies provided sex-segregated data, these methodological differences and their impact on sex effects could have been examined quantitatively. We encourage researchers to report these data, as well as potential moderating factors, so that the role of sex differences can be better understood.

Translational Significance This article highlights the lack of evidence on how sex may influence the potentially modifiable relationship between depression and subsequent Alzheimer's disease, despite known sex differences in both dementia and depression. Based on an in-depth review of existing studies, suggestions for the design of future studies examining this important topic are provided.

Key words: Alzheimer's disease, Cognitive impairment, Dementia, Depression, Meta-analysis, Sex

Alzheimer's disease (AD) is the leading cause of dementia worldwide, making identification of potentially modifiable AD risk factors an important step toward reducing dementia-related burden in an aging population. Depression is one such risk factor (Diniz, Butters, Albert, Dew, & Reynolds, 2013) and multiple potential mechanisms for this association have been proposed (Byers & Yaffe, 2011; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Given there are available treatments for depression, and evidence that treating depression reduces the risk of AD (Bartels et al., 2018), a better understanding of the mechanisms underlying the association between depression and AD risk could have considerable implications for the prevention of AD.

AD and depression are both more common in women (Cahill, 2006; Mielke, Vemuri, & Rocca, 2014), but findings of sex differences in the association between history of depression and AD are inconsistent. Men with depression have been found at greater risk for AD (Dal Forno et al., 2005; Fuhrer, Dufouil, & Dartigues, 2003) but other studies report women with depression are at greater risk for AD (Kim et al., 2015). Studies also vary considerably in methods of participant recruitment, length of follow-up and cognitive status of patients at baseline. In light of these inconsistencies, our goal was to conduct a systematic review and meta-analysis to better understand the role of sex differences in this relationship, as well as the potential role of moderating factors.

Method

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). Details regarding the search strategy can be found in Supplementary File 1.

Data Sources

MEDLINE, PsycINFO, and Cochrane Reviews were searched on January 10, 2018. Subject headings (e.g., MESH terms) and keywords for depression, dementia, and epidemiologic studies of risk, incidence or prevalence were used, including all subkeywords nested under these keywords in their respective databases.

Study Selection Criteria

For the systematic review, we included studies that met the following five criteria: (a) assessed the history of depression in both males and females at some time before the clinical diagnosis of AD; (b) used validated measurement tools or validated clinical diagnostic criteria for depression and for AD; (c) included a healthy control group of similar age, recruited from the same source, with no history of depression; (d) used a case–control or cohort study design; and (e) provided sex-segregated results of statistical analyses of the association between depression and subsequent AD, results of sex as a covariate in this association, or results of separate analyses of this association for men and women. For the meta-analysis, in addition to these five inclusion criteria, we included only studies that provided sufficient information to allow us to calculate unadjusted odds ratios (ORs) or risk ratios (RRs) for the risk of developing AD in men and women with a history of depression.

Article Screening and Data Abstraction

Abstracts were independently screened by HD and AA. Full texts of the remaining articles were reviewed independently by HD, AA, EU and another trained research assistant, with each study being screened by two reviewers. Discrepancies were discussed by all four raters and resolved by MCT.

To address the exposure and outcome of interest, data were extracted on the number of men and women who did or did not have a history of depression, and who did or did not go on to develop AD. If these raw data were not provided, unadjusted ORs or RRs for men and women were extracted. Data were also extracted to examine the influence of potential moderating variables, including method of patient recruitment (clinic or community-based sample); study design (case–control, or prospective or retrospective cohort); lifetime age of onset of depression; length of follow-up interval between depression and AD; manner in which depression and AD were diagnosed or measured (i.e., clinical diagnosis or a cutoff on a validated scale); clinical expertise of the individual(s) who made diagnoses (e.g., neurologist, psychiatrist, trained research assistant); and cognitive status of the sample at baseline (e.g., cognitively normal, mild cognitive impairment). We also recorded whether completion of neuroimaging (e.g., MRI) or biomarker (e.g., CSF) procedures or autopsy was an inclusion criterion for the study, as agreement to these procedures may differentially influence the participation of men and women.

Data Synthesis

Inter-rater agreement of studies included in the review was assessed using the Kappa statistic. For the meta-analysis, unadjusted RRs were used to quantify the association between depression and dementia in cohort studies, and unadjusted ORs were used to quantify this association in case–control studies. If not provided by authors, we calculated these unadjusted RRs or ORs from raw data for males and females separately within each study. If appropriate, random-effects meta-analysis models were used to compute pooled effect sizes. Sex differences were assessed using Cochran's $Q_{between}$ chi-squared statistic to compare the ratios for men and women in each study.

Results

Data Sources and Study Selection

The literature search returned 9,440 abstracts (Figure 1). Of these, 3,619 full text articles were screened for eligibility and 40 met the first four inclusion criteria for the systematic review. These 40 studies comprised a total of 47,342 males and 62,729 females. Of these 40 studies, seven met the fifth inclusion criterion allowing them to be included in the qualitative synthesis (Figure 1). These seven studies are described in Table 1. Only three of these seven met the criterion required for the meta-analysis (Figure 1) and thus, we were unable to conduct the analysis. Agreement between the four raters was good (κ = .76).

Qualitative Synthesis

Of the seven studies included in the qualitative synthesis, three provided sufficient information to allow us to calculate unadjusted ORs or RRs in men and women (Bartolini et al., 2005; Dal Forno et al., 2005; Lara et al., 2016), two provided the results of separate regression analyses for males and females (Fuhrer et al., 2003; Kim et al., 2015), and two provided the results of sex as a covariate in their regression analyses, which were also adjusted for other variables (Chen et al., 1999; Vilalta-Franch et al., 2013; Table 1). All seven studies used prospective cohort designs. Two studies found a significant association between depression and subsequent AD in men only (Dal Forno et al., 2005; Fuhrer et al., 2003), while two found a significant

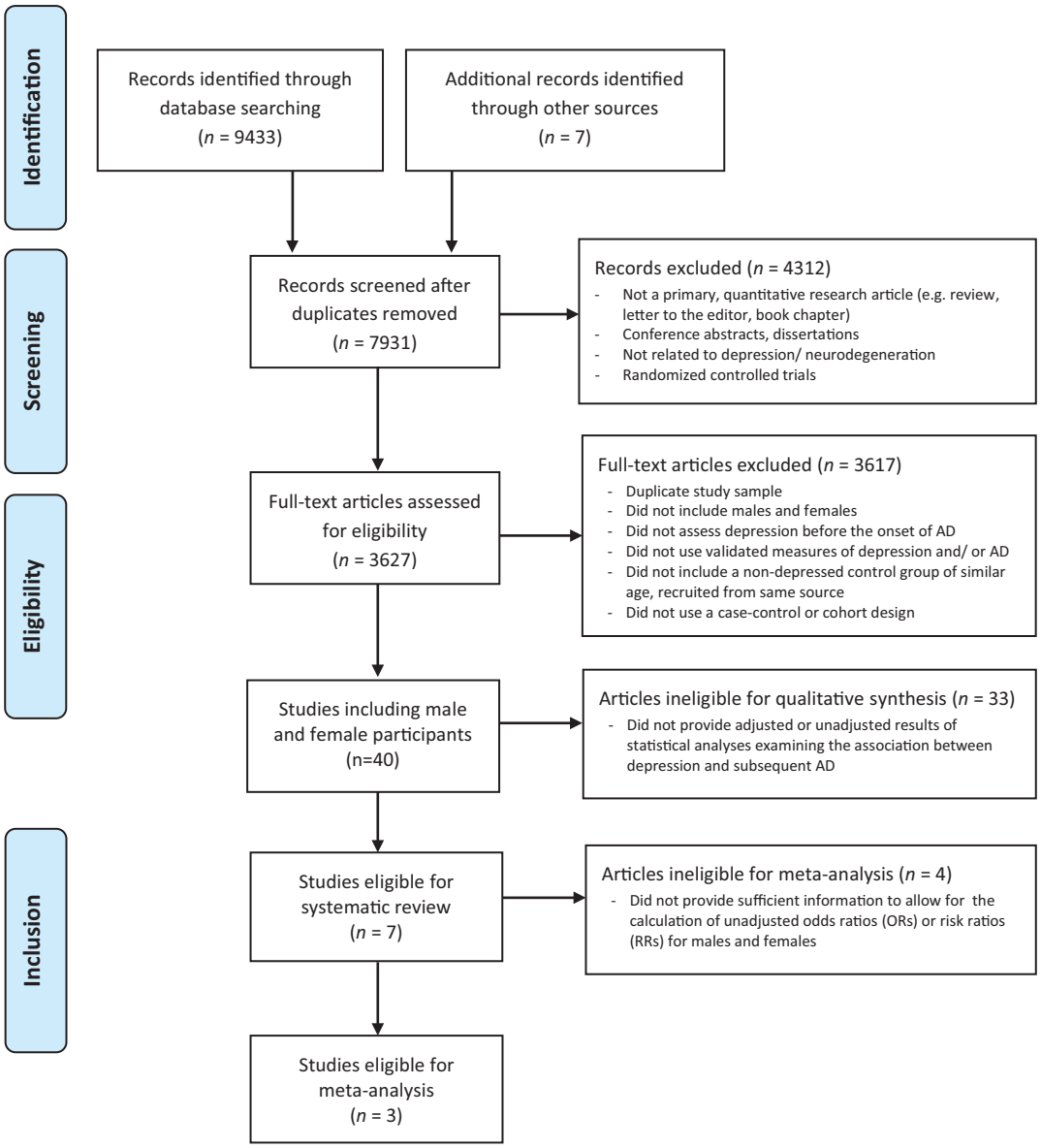

Figure 1. PRISMA flow chart of reviewed studies.

Table 1. Characteristics of Included Studies

Study	Country	Type of sample	Diagnosis of depression at baseline	Diagnosis of incident AD at follow-up	Cognitive status at baseline	Sample size	% Female	Mean age at baseline (years)	Mean follow-up duration (years)	Maximum follow-up duration (years)	Mean education (years)	Adjustments of ORs or RRs	Findings
Chen, Ganguli, Mulsant, and DeKosky (1999)[b]	United States	Community	DSM-III-R	NINCDS-ADRDA	Nondemented	803	60	73.7	4.5[a]	8	61.4% graduated high school	Age, sex, education	No significant relationship, no effect of sex
Fuhrer and colleagues (2003)[b]	France	Population	CES-D ≥ 17 men, ≥ 23 women	DSM-III-R, NINCDS-ADRDA	Nondemented	3,777	58	M: 74.5 F: 75.7	8	8	NS	Age, education, MMSE	Significant in men only
Bartolini, Coccia, Luzzi, Provinciali, and Ceravolo (2005)[c]	Italy	Clinic	DSM-III-R	NINCDS-ADRDA	Subjective cognitive complaints but normal neuropsychological test scores	222	64	69.2	1	1	6.9	Unadjusted	Significant in women only
Dal Forno and colleagues (2005)[c]	United States	Community	CES-D ≥ 16	DSM-III, NINCDS-ADRDA	Nondemented	1,357	42	M: 66.8 F: 64.0	—	14	M: 17.1 F: 16.3	Unadjusted	Significant in men only
Vilalta-Franch and colleagues (2013)[b]	Spain	Population	DSM-IV	DSM-IV	Nondemented	451	65	76.9	5	5	4.2	Age, sex, marital status, education, MMSE, stroke history, executive function subscale of CAMCOG	Significant relationship, no effect of sex
Kim and colleagues (2015)[b]	South Korea	Clinic	SGDS-K ≥ 8	NINCDS-ADRDA	MCI	294	66	M: 73.0[a] F: 72.0[a]	1.2[a]	3	M: 14.0[a] F: 6.0[a]	Age, education, MMSE, CDR, HIS, vascular risk factors, APOE e4, WMH	Significant in women only
Lara, Haro, Tang, Manly, and Stern (2016)[c]	United States	Community	DSM-V	DSM-V	Nondemented	1,748	67	77.0	5.6	14.4	10.3	Unadjusted	Significant relationship, no sex difference

Note. DSM (versions III, IV, V, R, revised) = diagnostic and statistical manual of mental disorders; CES-D = Center for Epidemiological Studies Depression Rating Scale; SGDS-K = Korean version of the Geriatric Depression Scale short form; NINCDS-ADRDA = National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's disease and Related Disorders Association criteria for the diagnosis of AD; MCI = mild cognitive impairment; NS = not stated; MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Cognitive Examination; CDR = Clinical Dementia rating; HIS = Hachinski Ischemic Score; WMH = white matter hypertensitie.

[a]Median.

[b]Provided results (i.e., ORs or RRs) adjusted for other variables.

[c]Provided sufficient information to allow calculation of unadjusted odds ratios (ORs) or risk ratios (RRs).

association in women only (Bartolini et al., 2005; Kim et al., 2015). Two found a significant association between depression and AD but no effect of sex (Lara et al., 2016; Vilalta-Franch et al., 2013), and one found no significant association between depression and AD (Chen et al., 1999). Only one study provided data related to lifetime age of depression onset (Vilalta-Franch et al., 2013), but this study did not examine sex differences in the association between this variable and subsequent dementia.

We examined differences among the seven studies to potentially account for these inconsistent findings. The two studies which found the association to be significant in women only were unique in that they were the only studies where recruitment was clinic based, while all other studies used community- or population-based recruitment methods. Specifically, participants in these two studies were being seen in a clinical setting for cognitive complaints (Bartolini et al., 2005) or mild cognitive impairment (Kim et al., 2015) at baseline. Moreover, the two studies finding an association in women only had the shortest mean follow-up durations (1 and 1.2 years) of all seven studies. These two methodological aspects are likely related, in that shorter follow-up would be required to detect incident dementia in clinical populations already showing early cognitive changes than would be required in population- or community-based samples. Another methodological difference among the seven studies is the manner in which depression was measured and defined. The two studies that found a significant association between depression and subsequent AD in men only (Dal Forno et al., 2005; Fuhrer et al., 2003) both used cutoff scores on self-report measures of depression, whereas the three studies that found no sex differences (Chen et al., 1999; Lara et al., 2016; Vilalta-Franch et al., 2013) all used clinical diagnostic criteria to diagnose depression. The two studies that found an association in women but not in men differed in the methods used to classify depression, with one using cutoffs on a self-report depression scale (Kim et al., 2015) while the other used clinical diagnostic criteria (Bartolini et al., 2005). Thus, among the seven included studies, these two approaches to defining depression did not appear to lead to consistent findings regarding sex differences.

Discussion

To the best of our knowledge, this is the first systematic review of sex differences in depression as a risk factor for AD. Of 40 studies including a large number of both male and female participants and examining depression as a risk factor for AD, only seven provided sufficient information for a qualitative synthesis. Even fewer studies (three) reported the necessary sex-segregated data required for a meta-analysis, and thus we were unable to conduct one. The findings of our review are consistent with previous meta-analyses (Diniz et al., 2013; Ownby et al., 2006) which found that depression is a risk factor for AD and other dementias, and extend these findings by exploring sex differences in this relationship.

Our qualitative synthesis revealed several aspects of the methodological approaches used in these seven studies which may contribute to the differences in findings and should be considered in future research. AD was more likely to occur in women than men when the study sample was comprised of patients who were being seen in a clinical setting for subjective or objective cognitive impairment at baseline. Likely related to these baseline characteristics, the studies finding an association between depression and subsequent AD in women and not men also had the shortest follow-up durations. However, these findings may have been confounded by other factors influenced by the sex of the patient, including clinical referral patterns and willingness to attend specialty clinics for memory concerns, making it difficult to determine whether they are due solely to a sex differences in the association between depression and dementia. Given these potential biases and confounds, future studies should focus on recruitment of population- or community-based samples. Studies also varied in terms of how they defined or classified depression, which likely contributed to the inconsistent findings. It has been previously suggested that sex differences in the manner in which participants respond to self-report depression scales may result in a stronger association between prior depression and subsequent AD in men than in women (Dal Forno et al., 2005). Our systematic review did not fully support this, however. While two of the three studies that used cutoff scores on self-report depression scales did find a stronger association in men, the third found a stronger association in women. These findings suggest that both comprehensive diagnostic criteria for depression as well as validated depression scale cutoffs should be used in future studies. Future longitudinal work should consider whether there are sex differences in the duration between the age of onset of AD and the lifetime age of onset of depression. Previous work has suggested that lifetime age of depression onset may provide important insights into the nature of the association between depression and dementia (Singh-Manoux et al., 2017). Unfortunately, we were not able to examine potential sex differences in our review because only one study provided data on the lifetime age of depression onset (Vilalta-Franch et al., 2013).

This review is limited by the lack of sex-segregated data provided by studies which met inclusion criteria. The lack of available sex-segregated data for a meta-analysis is not a unique problem—the paucity of literature on sex differences in neurodegeneration has been reported in other systematic reviews. For example, a review of clinical trials of cholinesterase inhibitors found no studies presenting sex-segregated data on the efficacy, safety, and tolerability of these drugs, despite animal models demonstrating that sex may modify cholinesterase inhibitor treatment response (Canevelli et al., 2017). Without these data, it is impossible to quantitatively synthesize the existing literature on sex

differences in these areas, limiting our ability to fully understand these associations (Cahill, 2006).

Of the seven studies that did provide the sex-segregated data required to be included in our systematic review, four of these studies were limited in that they did not report raw sex-segregated data and thus we had to rely on the significance of ORs or RRs which had been adjusted for other covariates in the models examining the association between depression and subsequent AD. Additionally, these four studies were not consistent in terms of the covariates included in these analyses, rendering caution in comparisons across studies. This emphasizes the importance of not only providing raw sex-segregated data, but also of providing raw data on potential covariates so that they all can be examined in meta-analyses.

In conclusion, the findings of our systematic review indicate that, despite the body of literature showing important sex and gender differences in neurodegeneration and aging (Cahill et al., 2006), many studies fail to report and examine these differences, even though the data are available to do so. Our qualitative synthesis herein revealed inconsistent findings regarding sex differences in the association between depression and AD, but it also showed that there were important methodological differences among the available studies which report sex data. This clearly demonstrates the need for more longitudinal studies in this area using consistent approaches to recruitment and measurement. Given the potential to develop treatments for depression, which in turn could have implications for subsequent risk of AD, it is crucial to understand variables such as sex which may moderate this relationship. While it is encouraging that a relatively large number of studies have investigated the relationship between depression and subsequent AD, and 40 of these studies did include both males and females, authors need to report sex-segregated data so that meta-analyses are possible. We encourage authors to publish their sex-segregated data (ide their sex-segregated data in the form of supplementary tables), and to take sex into account as more than a covariate in future studies, so that researchers can make conclusions about how sex and depression interact to predict AD in our aging population.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

None reported.

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